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# Pill Heralds Biological Change

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THE INTRODUCTION of the pill—oral contraceptive drugs—is an innovation whose long-term biological, social, moral and religious effects are hard to foresee, except that they will be important.

While the population explosion in poor countries is an important motive for its development, the pill has found its quickest acceptance among affluent Americans. This part of the world also aspires to the highest standards of health, including safe drugs.

Because of the American initiative in its scientific development, the pill must meet the United States standards of health before it can be made available for more urgent application in helping to solve a world problem.

Our approach to this innovation should be an illuminating forerunner of what we can expect in the future from the impact of biological developments on society. The Hellman committee report on the pill is a source of many subjects on which I plan to comment from time to time. The purpose of the comment is not to give gynecological advice (on which I am no expert) but to provide consideration of the perplexities that impede reliable conclusions in human affairs.

## Prominence Beyond Importance

EMBOLISM IS the most notable of the specific lethal hazards that have been attributed to the pill. It is a mysterious clotting of the blood that has a dangerous effect when the clots lodge in the lung or the brain.

The death of a young woman from

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embolism is even more tragically dramatic when it occurs suddenly with no premonitory symptoms. This gives individual cases a prominence beyond their statistical importance—a risk rate among young women of about 15 to 20 microdeaths (reported deaths per million per year). For perspective, compare this with the over-all population rates of 500 microdeaths from accidents and 49 from murder—keeping in mind that the latter figures are for everyone while the former is for only young women.

Drug manufacturers have systematically sought information on embolism among women taking the pill. They heard of only 13 lethal cases, or three microdeaths, in 1965. The Hellman report does not infer that embolic disease is caused or not caused by the pill, but that cases were grossly underreported, which is probably true.

The report finds no important fault in the drug companies' procedures, but rather in the fundamental process by which information can be obtained from physicians about individual patients' deaths under specific therapy. But then if we take a properly rigorous view of the statistics, we should assert that no conclusion at all is justified.

This point should not be misunderstood. There is no greater or lesser justification for associating the pill with embolic disease than with, say, lung cancer, heart disease or alcoholism—but no outstanding hazard has been found.

The report concludes that: "The data derived from mortality statistics are not adequate to confirm or refute the role of oral contraceptives in thromboembolic disease. They do, however, suggest that if oral contraceptives act as a cause they do so very infrequently rela-

tive to the number of users. The task force believes, nevertheless, that the only way in which this question can be answered definitively is through well-controlled epidemiological studies."

## Impossible to Prove

THE MOST COGENT challenge that emerges from the report is the need to do something about our helplessness in attempting reliable judgments about low-level risks in the existing framework of disease statistics.

Even with the most extensive statistics, it will be logically impossible to prove that a drug is absolutely safe. Whatever sample groups are used for preliminary tests, personal idiosyncrasies may still be found in other segments of the population. These may be based on genetic differences, diet, other medication, or existing or past disease.

The most extensive analysis can only reduce the imprecision of our knowledge about the risk. We must then balance the range of possible risk, never precisely zero, against the intended advantages and against the other risks of everyday life. Because the pill is not a life saving drug, personal judgments will play an unusual role in the final conclusion about the desirability of using it.

Obtaining the statistics of rare events requires an enormous investment in the careful observation of clinical trials. To prove that the pill is no more dangerous than pregnancy required a study of at least 20,000 women-years of exposure, and this was achieved after the pill was generally available. However, a detailed follow-up on many tens of thousands of cases is needed to exclude more diffuse effects—good or bad—on general patterns of health and survival, especially over longer periods of time.